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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR             | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/778,259      | 02/07/2001  | Cristobal Guillermo dos Remedios | 13388               | 4496             |

7590 09/11/2007  
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Garden City, NY 11530

| EXAMINER |
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CHEU, CHANGHWA J

| ART UNIT | PAPER NUMBER |
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1641

| MAIL DATE | DELIVERY MODE |
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09/11/2007

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

## Office Action Summary

Application No.

09/778,259

Applicant(s)

REMEDIOS ET AL.

Examiner

Jacob Cheu

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 25 June 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 38 and 42-47 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 38, 42-47 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☒ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date 9/10/07
- ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- ☐ Notice of Informal Patent Application
- ☐ Other: \_\_\_\_\_

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.
2. Applicant's amendment filed on 6/25/2007 has been received and entered into record and considered.

The following information provided in the amendment affects the instant application:

Claims 1-37, 39-41 are cancelled.

Claims 46-47 are added.

Currently, claims 38, 42-47 are under examination.

### *Claim Rejections - 35 USC § 103*

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.
2. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:
  1. Determining the scope and contents of the prior art.
  2. Ascertaining the differences between the prior art and the claims at issue.
  3. Resolving the level of ordinary skill in the pertinent art.

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4. Considering objective evidence present in the application indicating obviousness or nonobviousness.
3. The rejections of claim 38, 42-43, 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. (J. Inorganic Biochemistry 1998 Vol. 71, page 1-6) in view of Pisanti et al. (Marine Pollution Bull (1988) Vol. 19, page 328-333) are maintained.

With respect to claims 38, 42 and 47, Liu et al. teach a method of measuring fluorescence quenching of DNA bound fluorescence dye, e.g. increase dissociation or inhibition of fluorescent dye bound to the DNA, by a sample containing a metal ion, i.e. copper (II) (See abstract). Liu et al. teach that the presence of copper (II) metal would compete with binding the DNA molecule intercalated with the fluorescence ethidium dye (See abstract; Results and Discussion). The binding constant of the copper is around  $10^{-10}$  ( $M^{-1}$ ) which falls within the range of micromolar (See Figure 1). However, Liu et al. do not explicitly teach detecting the inhibition or dissociation of the dye on the DNA as an indication of the presence of a metal in the environment, such as aquatic, terrestrial or industrial samples.

Pisanti et al. teach the presence of metals in the ecosystem, e.g. ocean or rivers, is of great concern because of the potential to impact the quality and physiology of marine organisms (page 328, left column, first paragraph; page 330, right column, last paragraph). Pisanti et al. teach metal ion levels, such as copper, are essential for the biological equilibrium of the marine ecosystem. Supra.

Therefore, it would have been obvious to one ordinary skill in the art at the time the invention was made to have motivated Liu et al. to measure the presence of copper in an aquatic sample as taught by Pisanti et al. with reasonable expectation of success because monitoring copper metals in the environmental is of great concern for maintaining quality of ecosystem, and Liu et al. has developed an effective fluorescence quenching assay by the heavy metal, such as copper (II), and such assay would be useful and capable of

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detecting the presence of copper heavy metal in the environment by screening either dissociation of binding between the nucleic acid and the dye by the copper metal ion compound.

With respect to claim 43, Liu et al. use ethidium bromide as the fluorescence dye (See page 2, Section 2.1 Materials and Methods).

4. The rejections of claim 44-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. in view of Pisanti et al. and further in view of Gold et al. (US 624246) are maintained.

Both Liu et al. and Pisanti et al. references have been discussed but are silent in teaching use of a solid support for immobilization of DNA for analysis.

Gold et al. teach an efficient and sensitive screening for DNA binding agents by immobilizing DNA on solid support and measuring the change of dye, e.g. fluorescence, for indicative of the presence of the binding agent (Col. 13, line 25-345; Figure 4-5).

Gold et al. teach a variety of choices for solid support, including glass, polystyrene, gold or silicon (Col. 6, line 42-50).

Therefore, it would have been obvious to one ordinary skill in the art at the time the invention was made to have provided both Liu and Pisanti et al. with the solid support for immobilization of DNA for better efficiency since it is well-known for immobilization of molecule on a solid support to increase sensitivity of the assay and the methodology employed by Gold et al. in also in an analogous field, e.g. measuring change of fluorescence dye for indicative of DNA binding agents.

***Response to Applicant's Arguments***

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Applicant argues that Liu et al. reference distinguishes from the instant invention because Liu et al. reference uses copper (II) macrocyclic complex, whereas the instant invention detects metal ion that is free of macrocyclic compound. Applicant also argues that Liu et al. reference does not directly detect a metal atom that exists in the environment (See Exhibit A and Exhibit B).

Applicant arguments have been considered, but are not persuasive.

It is noted that the recited “metal atom” encompasses two states, namely “heavy metal” and “heavy metal ion” (See dependent claim 42)(emphasis added). Furthermore, the active step recites in claim 38 using “comprising” open language which does not exclude other material such as macrocyclic complex with copper (II) ion taught by Liu et al. reference. The claim does not recite the limitation “free of macrocyclic complex” as argued by the applicant. Therefore, teachings of Liu et al. still encompass the recited features. With respect to “direct” measuring of heavy metal, this specific limitation does not appear in the claim language. In addition, conducting the assay taught by Liu et al., as long as the quenching is detected, this observation would reflect the amount of metal copper (II) in the environment.

Applicant also argues that the detection threshold on the metal in reference of Liu et al. is very sensitive for very low, nontoxic levels, whereas the instant invention would detect more higher levels of metal in the environment, thus this feature distinguishes the Liu et al. reference.

Applicant arguments have been considered, but are not persuasive.

It is noted that the preamble of the recited method detects “micromolar amounts a toxicant”, “micromolar” is a low level of concentration. Absence of evidence to the contrary, applicant had not submitted evidence that the detection level in Liu et al. would be lower than the “micromolar” range, e.g. in ‘picmolar’ range sensitive than the current

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invention. Therefore, the assay taught by Liu et al. would be capable of detecting the micromolar range of metals in the sample.

Applicant also argues that the secondary reference Pisanti et al. merely teaches that the presence of metals in the ecosystem is of great concern and that the metal levels are essential for the biological equilibrium of the ecosystem. Applicant argues that this reference does not obviate the deficiencies of the primary reference to Liu et al.

Applicant arguments have been considered, but are not persuasive.

As indicated in the previous and the present Office Action, Pisanti et al. provided the motivation and suggestion to one ordinary skill in the art to combine the teachings of Liu et al in measuring the environmental heavy metal contamination, e.g. copper. Liu et al. reference discloses that copper metal would quench, e.g. dissociation, the fluorescent dye intercalated from DNA molecules. The assay of Liu et al. can be used to detect metals in the sample. Pisanti et al. disclose that heavy metal contamination, such as copper, is of great public health concern. Thus, it would not be improper to combine these two references since Pisanti et al. provides the motivation and suggestion to apply the method taught by Liu et al. to detect metals in the environmental samples, such as aquatic, terrestrial or industrial samples.

### ***Conclusion***

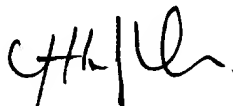
5. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jacob Cheu whose telephone number is 571-272-0814. The examiner can normally be reached on 9:00-5:00.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Jacob Cheu  
Examiner  
Art Unit 1641

August 31, 2007

  
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